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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/931,732 | 08/16/2001 | Bob D. Brown | OASBIO.001C1 | 4615 |

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| EXAMINER | |
|---|---|
| ASHEN, JON BENJAMIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/931,732 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | Jon B. Ashen | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12 and 20-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 20-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/29/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/19/2005 has been entered (in part: see below).

### *Status of Application/Amendment/Claims*

***2.*** Claims 1-12 and 20-36 are pending in this application. Claims 13-19 were cancelled by Applicant in the communication filed 8/19/2005.

Applicant's response filed 8/16/2005 has been fully considered. Rejections and/or objections not reiterated from the previous office action mailed 05/17/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Specification*

3. The amendment filed 8/16/2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

On pg. 2 of the instant amendment, Applicant has indicated that lines 21-23 on pg. 3 of the specification as filed are to be deleted. However, the response fails to point to any particular support for the deletion of this text, which appears as part of the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites, "wherein said antisense oligonucleotide comprises one or more sequence motif with one or more degenerate and/or universal base." However, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption, because there is no context in claim 20, for

determining what would be encompassed by a "sequence motif" or for determining if the claimed one or more universal or degenerate base is required to be in the claimed sequence motif vs. in the antisense oligonucleotide itself, for example. Claims 21 and 22 are rejected due to their dependence on a rejected claim.

6. Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 35 is generally narrative and indefinite, failing to conform with current U.S. practice, in particular because it is not a complete sentence. Therefore, the skilled artisan cannot determine the metes and bounds of what is being claimed with this terminology, without assumption. Claim 36 is rejected due to dependence on a rejected claim.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12 remain rejected and 20-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record as set forth in the Office Action mailed 5/17/2005 and restated below. The claim(s) contains subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

***Response to Arguments***

9. Applicant's arguments filed 8/16/2005 have been fully considered but they are not persuasive. Applicant has argued, with regards to claims 1-6, that the claims as amended are drawn to improved antisense, that as such, they acknowledge that antisense oligonucleotide are known in the art and indicate that the claimed improvements include the claimed modifications recited in the present claims and that therefore the skilled artisan readily appreciates the structure of antisense oligonucleotides in the prior art and the improvements described in the specification and recited in the claims (pg. 11). Applicant has pointed to the recitation, in the claims, of particular compounds that are non naturally occurring bases and argued that these elements are chemical structures that are provided for use with the antisense oligonucleotides in the specification and to the recitation, in the claims, of an RNase H recruiting region that is disclosed as a structural element in the specification (pg. 11). With regards to claims 7-12, Applicant has argued that the claims are fully described because guidance to specific RNase recruiting regions and targeting regions are provided in the specification and one of skill would readily appreciate the structural elements that are recited in the claims. Applicant has pointed to the disclosures in the specification, of particular structural elements including RNase L and P recruiting

regions, compounds that are non naturally occurring bases and the discussion of ribozyme targeting regions as conveying to one of skill that applicant has possession of the claimed invention (pgs 12-13).

However, contrary to Applicants assertions, the basis of the outstanding rejection under 35 U.S.C. § 112 1st paragraph, written description, considers that Applicant has not reasonably conveyed to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention because the specification does not provide or point to a specific structure that corresponds with the function of being antisense or acting as a ribozyme against at least two RNA molecules of different sequence, as claimed. Applicant, is correct, in part in asserting that antisense oligonucleotides, in general, are known in the prior art. However, reliance on the general teachings in the art of antisense, the general listing of non-naturally occurring bases that can be included in the claimed antisense oligonucleotides and the general disclosure the structural requirements for constructing antisense oligonucleotide with an RNase H recruiting (or other RNase recruiting region; e.g., L or P), and the general disclosure of what is required in determining the target site of a ribozyme is insufficient to overcome the outstanding grounds of rejection which considers that the structures disclosed by Applicant are not correlated with the function of being antisense or acting as a ribozyme against at least two RNA molecules of different sequence, as claimed.

Applicant has provided examples of gene sequences known in the art to comprise nucleotide mismatches due to mutation and asserted that antisense

oligonucleotides that are targeted to these regions will function as antisense. Applicant has provided no evidence of this antisense function for any of their disclosed oligonucleotides and no evidence that they were in possession of a particular antisense oligonucleotide or ribozyme that has the broadly claimed function of hybridizing to any two RNA molecules that that differ in sequence by one or more nucleotide mismatch in the hybridized target regions and function as antisense.

Therefore, Applicant has not provided adequate written description of their invention because Applicant has not indicated that they were in possession of the instant invention commensurate with the breadth of what is claimed, such as by providing a correlation between the structure of the broad genera of antisense oligonucleotides and ribozymes now claimed and the function of being an antisense oligonucleotide or ribozyme that will hybridize to any two RNA molecules that differ in sequence by one or more nucleotide mismatch in the hybridized target regions and mediate the degradation of both RNAs. Claims 20-34 are rejected due to their dependence on a rejected claim.

***Claim Rejections - 35 USC § 102***

***Withdrawn***

10. Applicants amendments to claims 1-8, 11,12 and 20-22 is sufficient to overcome the outstanding grounds of rejection under 35 U.S.C. 102(b) as being anticipated by Cook et al., Torrence et al., Stinchcomb et al. and Bennett et al., as set forth in the Office Action mailed 5/17/05.

***New Rejections***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-6, 20-25 and 29-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Nyce (WO 99/13886 A1 which is Reference 60 on PTO Form 1449 filed 8/28/2002).

The instant claims are drawn to an antisense oligonucleotide between 6 and about 50 bases in length that comprises one or more non-naturally occurring backbone linkage and one or more non-naturally occurring base selected from degenerate bases, 5-nitroindole, 3-nitropyrrole, 4-nitroimidazole and nebularine wherein the antisense oligonucleotide is able to hybridize to two or more RNA molecules that differ in sequence by one or more nucleotide mismatch in the hybridized target regions and wherein the one or more non-naturally occurring base is positioned in the antisense oligonucleotide to align with a nucleotide mismatch position in the target regions of the RNA molecules (claim 1), an antisense oligonucleotide comprising a RNase H recruiting region and a non naturally occurring base as required by claim 1 (claims 3 and 5), an antisense oligonucleotide comprising an RNase L recruiting region comprising a 2'-5' adenosine oligomer and a non-naturally occurring base as required by claim 1 (claim 7), an antisense oligonucleotide comprising an RNase P recruiting region and a non-

naturally occurring base as required by claim 1 (claim 9), and a ribozyme comprising a non-naturally occurring base as required by claim 1 (claim 11). Dependent claims 2 and 4 specify that the antisense oligonucleotides of claims 1 and 3 can have no more than about 50% universal and/or degenerate bases. Dependent claims 6, 8, 10 and 12 specify that the RNA targeting regions of the antisense oligonucleotides of claims 5 , 7 and 9 and the ribozyme of claim 11 can have no more than about 50% universal and/or degenerate bases. Dependent claims 20-34 require that the antisense oligonucleotide of claim 1 comprise sequence motifs that are CG or poly G (claims 20-22) and the further limitations that the antisense oligonucleotides of claims 1, 3, 5, 7 and 9 and the ribozyme of claim 11 further comprise a universal base or an inosine base positioned on the respective antisense oligonucleotide or ribozyme to align with a nucleotide mismatch of the RNA target region.

Nyce discloses antisense oligonucleotides that bind to two or more RNA targets that comprise RNA targeting regions and can be constructed of DNA residues, thereby comprising DNA:RNA hybrid regions that are RNase H recruiting regions (pg. 3, pg. 16, which discloses deoxy residues that are contemplated in the construction of the claimed antisense oligonucleotides). The antisense oligonucleotides of Nyce are designed by substitution of no more than 5% of the adenosine bases with non-naturally occurring bases including 3-nitropyrrole (pg. 12, lines 5-27). Nyce discloses numerous examples of multi-target antisense oligonucleotides that are able to hybridize to two or more RNA molecules that differ in sequence by one or more nucleotide mismatch in the hybridized target regions and wherein the non-naturally occurring base is positioned to align with a

nucleotide mismatch in the hybridized target regions (pgs. 9-13 and Table 3 and 4 (see pgs 73-77 for tables). Nyce discloses modifications of phosphodiester residues of the antisense oligonucleotide including methylphosphonate and phosphorothioate internucleoside linkages (pg. 15, 2nd full paragraph). Nyce discloses that the antisense oligonucleotides of his invention can comprise universal bases that are substituted for any other base including inosine and degenerate bases (pg. 12). The antisense oligonucleotides of Nyce comprise sequence motifs that are CG and poly-G (see table 3, pgs 73-76).

Therefore, Nyce anticipates the instant invention as set forth in claims 1-6, 20-25 and 29-32.

***Claim Rejections - 35 USC § 102 or 35 USC § 103***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> ((b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-6, 20-25 and 29-32 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Bergstrom et al. (U.S. Patent 5,681,947) (Reference 22, PTO Form 1449 filed 8/28/02). The invention as set forth in claims 1-6, 20-25 and 29-32 is outlined above.

Bergstrom et al. disclose oligonucleotides that comprise universal bases in degenerate positions wherein the universal bases can be 3-nitropyrrole or inosine and that the oligonucleotides of their invention will hybridize to degenerate or ambiguous target sequences. In being formulated of DNA, the oligonucleotides of Bergstrom et al. comprise RNase H recruiting regions (pg. 3, lines 42-45; col. 4, lines 10-20; cols. 7-9 and Table 1). Bergstrom et al. disclose therapeutic applications for oligonucleotides comprising universal bases such as incorporation into triplex forming oligonucleotides and in antisense oligonucleotide therapeutics directed toward nucleic acid targets which have significant variability (col. 8). The oligonucleotides of Bergstrom et al. hybridize to 2 RNA molecules of different sequence in targeting degenerate RNA transcripts and the universal bases of Bergstrom et al. that are disclosed as being in degenerate positions, are located in the RNA target regions and aligned with mismatches on both targeted RNAs.

Furthermore, since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotide comprises, absent evidence to the contrary, an antisense oligonucleotide as claimed. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA

1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Therefore, the instant invention is anticipated or obvious over Bergstrom et al. (U.S. Patent 5,681,947).

15. Claims 1-6 and 20-25 are rejected under 35 U.S.C. 102(b) or 35 USC 103(a) as being anticipated by or obvious over Guo et al. (WO 97/46711 which is Reference 59, PTO Form 1449 filed 8/28/02). The invention as set forth in claims 1-6, 20-25 and 29-32 is outlined above.

Guo et al. disclose oligonucleotides that comprise universal bases in degenerate positions and that include artificially synthesized mismatches wherein the universal bases can be 3-nitropyrrole. The oligonucleotides of Guo et al. hybridize to 2 RNA molecules of different sequence in targeting allelic transcripts and the universal bases of Guo et al. that are disclosed as being in degenerate positions, are located in the RNA target regions and aligned with mismatches on both targeted RNAs. The oligonucleotides of Guo et al. comprise RNase H recruiting regions because they are formulated from DNA and will form DNA:RNA hybrids which will recruit RNaseH (pg. 3, line 10 to pg. 5, line 15; pg. 8, Figures 1, 4 and 5).

Furthermore, since the prior art oligonucleotide meets all the structural limitations of the claims, the prior art oligonucleotide comprises, absent evidence to the contrary,

an antisense oligonucleotide as claimed. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

Therefore, the instant invention is anticipated or obvious over Guo et al. (WO 97/46711).

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-12 and 20-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergstrom et al. (U.S. Patent 6,172,216) as applied to claims 1-6, 20-25 and 29-32 above, and further in view of Werther et al. (U.S. Patent 5,929,040, reference previously made of record in the Action mailed 10/20/2004), Torrance et al. (U.S. Patent 5,583,032, reference 15, PTO Form 1449 filed 8/28/2002) and Krupp (1993, reference 82, PTO-1449 filed 8/28/02).

The invention as set forth in the instant claims is drawn to an antisense oligonucleotide between 6 and about 50 bases in length that comprises one or more non-naturally occurring backbone linkage and one or more non-naturally occurring base selected from degenerate bases, 5-nitroindole, 3-nitropyrrole, 4-nitroimidazole and nebularine wherein the antisense oligonucleotide is able to hybridize to two or more RNA molecules that differ in sequence by one or more nucleotide mismatch in the hybridized target regions and wherein the one or more non-naturally occurring base is positioned in the antisense oligonucleotide to align with a nucleotide mismatch position in the target regions of the RNA molecules (claim 1), an antisense oligonucleotide comprising a RNase H recruiting region and a non naturally occurring base as required by claim 1 (claims 3 and 5), an antisense oligonucleotide comprising an RNase L

recruiting region comprising a 2'-5' adenosine oligomer and a non-naturally occurring base as required by claim 1 (claim 7), an antisense oligonucleotide comprising an RNase P recruiting region and a non-naturally occurring base as required by claim 1 (claim 9), and a ribozyme comprising a non-naturally occurring base as required by claim 1 (claim 11). Dependent claims 2 and 4 specify that the antisense oligonucleotides of claims 1 and 3 can have no more than about 50% universal and/or degenerate bases. Dependent claims 6, 8, 10 and 12 specify that the RNA targeting regions of the antisense oligonucleotides of claims 5 , 7 and 9 and the ribozyme of claim 11 can have no more than about 50% universal and/or degenerate bases. Dependent claims 20-34 require that the antisense oligonucleotide of claim 1 comprise sequence motifs that are CG or poly G (claims 20-22) and the further limitations that the antisense oligonucleotides of claims 1, 3, 5, 7 and 9 and the ribozyme of claim 11 further comprise a universal base or an inosine base positioned on the respective antisense oligonucleotide or ribozyme to align with a nucleotide mismatch of the RNA target region.

The teachings of Bergstrom et al. are set forth above.

Bergstrom et al. do not teach ribozymes as claimed or antisense oligonucleotides comprising RNase L or RNase P recruiting regions.

Werther et al. teach the construction of a multivalent antisense molecule that target at least two insulin growth factor binding proteins (IGFBP) (which encompasses IGFBP-2 and IGFBP-5) (column 3, lines 63-67, column 5, lines 30-35) and a method of inhibiting IGF-I mediated cell proliferation using "a polynucleotide capable of interacting

with mRNA directed from two or more of an IFG-I gene, an IFG-I receptor gene or a gene encoding an IFGBP such as IGFBP-2 and/or IGFBP-3 (column 4, lines 10-15). The prior art antisense oligonucleotide of Werther et al. is preferably 20-25 nucleotides in length (column 3, lines 34-35) and can be a ribozyme that targets one or more IGFBPs such as IGFBP-2 and/or IGFBP-3 (column 4, lines 40-45), may be constructed with a non-ionic or phosphorothioate backbone (column 3, lines 55-57) and can be constructed to be exactly complementary to a region of both IGFBP 2 and 3 or to contain one or more nucleotide substitutions, additions or deletions (col. 3, lines 40-45). Werther et al. teach benefit of targeting IGFBPs for ameliorating the effects of a proliferative and/or inflammatory skin disorder in a mammal because, "targeting these molecules (*IGF-I, IGF-I receptor and IGFBPs*) according to the methods contemplated herein provides the best results to date" (column 2, lines 35-39)

Torrance et al. teach the advantages of RNase L recruiting regions in antisense applications wherein they disclose chimeric antisense oligonucleotides that comprise 4, 2'-5' linked adenosines (an RNase L-recruiting region) and an a 3',5' – deoxyribonucleotide antisense sequence (an RNA targeting region) (column 24, example 7), show that 2-5A greatly enhances the ability of an antisense oligonucleotide to inhibit specific gene expression (column 33, lines 28-35) and teach that, "Because 2-5A-dependent RNase is believed to be present in most mammalian cells, the therapeutic control of protein translation for the treatment of cancer, viral infections, genetic diseases, osteoarthritis, rheumatoid arthritis, restinosis, and a variety of other

medical conditions can be accomplished using this technology" (column 34, lines 62-67).

Krupp teaches that advantages of RNase P in antisense applications wherein he recites, "[t]he RNase P approach can combine attractive features from both established systems: similar to ribozyme systems the free choice between extracellular addition of oligoribonucleotides or intracellular production of RNA transcripts; like the RNase H approach, it takes advantage of the efficiency of a normal cellular enzyme" (pg. 136, column 2, 3rd paragraph) and "RNase P combines the advantages of a ubiquitous cellular enzyme (like RNase H) with the possible choice between short, synthetic antisense oligoribonucleotides and large, in vivo RNA transcripts (like hammerhead ribozymes)" (pg. 138, conclusions, 1st paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, to construct a modified multivalent antisense oligonucleotide or ribozyme that was a degenerate modified multivalent antisense oligonucleotide or ribozyme targeted to IGFBP 2 and 3 that comprised a 3-nitropyrrole base in a mismatch position in order to target both IGFBP-2 and IGFBP-3 mRNA transcripts (as taught by Werther et al. and Bergstrom et al.), that also comprised an RNase L recruiting region or an RNase P recruiting region (as taught by Bergstrom et al., Torrance et al. and Krupp) in order to provide a degenerate multivalent antisense oligonucleotide that was more efficient at degrading multiple target mRNAs such that a more effective treatment of disease (proliferative or skin disorders) related to multiple RNA transcripts could be effected. It would have been obvious to construct the

antisense oligonucleotide above that further comprised inosine positioned to align with a nucleotide mismatch in the RNA target region in order to increase the ability of the degenerate multivalent antisense oligonucleotide or ribozyme to target multiple, degenerate or ambiguous targets (as taught by Bergstrom et al.).

One of ordinary skill in the art would have been motivated to construct a degenerate multivalent antisense oligonucleotide or ribozyme comprising one or more 3-nitropyrrole bases in a mismatch position in order to construct an antisense oligonucleotide or ribozyme therapeutic capable of interacting with mRNA directed from two or more of an IFG-I gene, an IFG-I receptor gene or a gene encoding an IFGBP such as IGFBP-2 and IGFBP-3 (as taught by Werther et al. and Bergstrom et al.), that also comprised RNase recruiting regions, because targeting multiple mRNA transcripts with a single oligonucleotide wherein the target region between the two RNAs differed by one or more mismatch (as taught for IGFBP 2 and 3 by Werther et al. above), was known in the art and because modifications to antisense oligonucleotides comprising the addition of an RNase L or P recruiting region were known in the art to provide the benefits of increased duplex stability as well as to operate by recruiting a naturally occurring enzyme such as an RNase L or P to greatly enhance the efficiency of the multivalent oligonucleotide to inhibit gene expression via the degradation of multiple target mRNA transcripts. One of ordinary skill in the art would have been motivated to construct the antisense oligonucleotide above that further comprised inosine positioned to align with a nucleotide mismatch in the RNA target region in order to increase the

ability of the degenerate multivalent antisense oligonucleotide or ribozyme to target multiple, degenerate or ambiguous targets (as taught by Bergstrom et al.).

One of ordinary skill in the art would have expected success in constructing a degenerate multivalent antisense oligonucleotide or ribozyme comprising one or more 3-nitropyrrole bases in a mismatch position because the prior art discloses that the substitution of 3-nitropyrrole bases in an oligonucleotide to allows hybridization of degenerate or ambiguous sequences (as taught by Bergstrom et al.). One of ordinary skill in the art would have expected success in constructing a degenerate multivalent antisense oligonucleotide or ribozyme as above that further comprised an inosine residue in positioned to align with a nucleotide mismatch in the RNA target region because this substitution was known in the prior art (as taught by Bergstrom et al.) to increase the ability of the degenerate multivalent antisense oligonucleotide or ribozyme to target multiple, degenerate or ambiguous targets. One of ordinary skill in the art would have expected success in constructing a degenerate multivalent antisense oligonucleotide or ribozyme as above that also had an RNase L or P recruiting region because the prior art shows the success of antisense oligonucleotide therapy using unmodified multivalent antisense oligonucleotides (Werther et al.) and each of the modifications taught by the prior art, as disclosed above, were known to be effective at enhancing the therapeutic effect of particular antisense oligonucleotide treatments (as taught by Torrence et al. and Krupp).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on Monday - Friday, 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 517-272-0811811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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